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(54) Title: TETRACYCLIC IMMUNOMODULATORY COMPOUNDS

(57) Abstract: The present invention relates to novel heterocyclic compounds, to methods for their preparation, to compositions containing them, and to methods and use for clinical treatment of medical conditions which may benefit from immunomodulation, including rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis. More particularly the present invention relates to novel heterocyclic compounds, which are CD80 antagonists capable of inhibiting the interactions between CD80 and CD28.

TETRACYCLIC IMMUNOMODULATORY COMPOUNDS

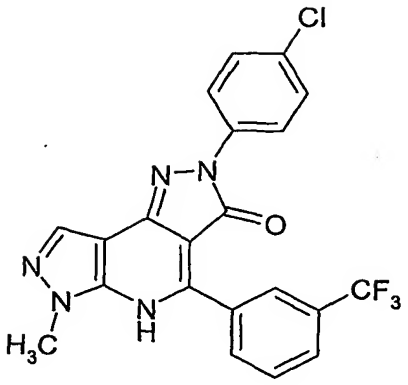
The present invention relates to novel heterocyclic compounds, to methods for their preparation, to compositions containing them, and to methods and use for clinical treatment of medical conditions which may benefit from immunomodulation, including rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis. More particularly the present invention relates to novel heterocyclic compounds, which are CD80 antagonists capable of inhibiting the interactions between CD80 and CD28.

Background of the invention

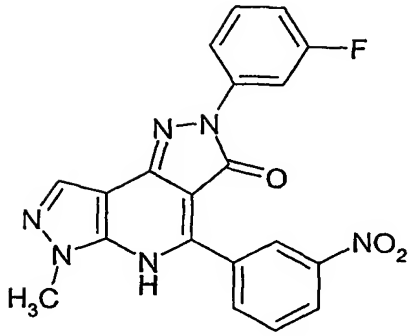
The immune system possesses the ability to control the homeostasis between the activation and inactivation of lymphocytes through various regulatory mechanisms during and after an immune response. Among these are mechanisms that specifically inhibit and/or turn off an immune response. Thus, when an antigen is presented by MHC molecules to the T-cell receptor, the T-cells become properly activated only in the presence of additional co-stimulatory signals. In the absence of accessory signals there is no lymphocyte activation and either a state of functional inactivation termed anergy or tolerance is induced, or the T-cell is specifically deleted by apoptosis.

One such co-stimulatory signal involves interaction of CD80 on specialised antigen-presenting cells with CD28 on T-cells, which has been demonstrated to be essential for full T-cell activation. (Lenschow et al. (1996) Annu. Rev. Immunol., 14, 233-258)

A paper by Erbe *et al*, in J. Biol. Chem. Vol. 277, No. 9, pp 7363-7368, describes three small molecule ligands which bind to CD80, and inhibit binding of CD80 to CD28 and CTLA4. Two of the disclosed ligands are fused pyrazolones of structures A and B:

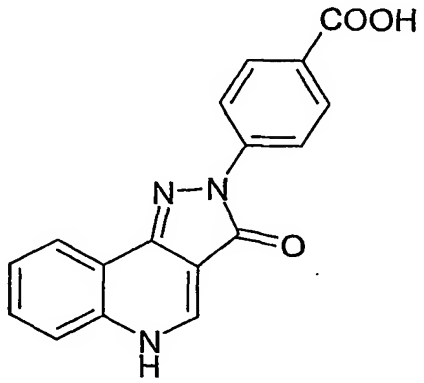


A



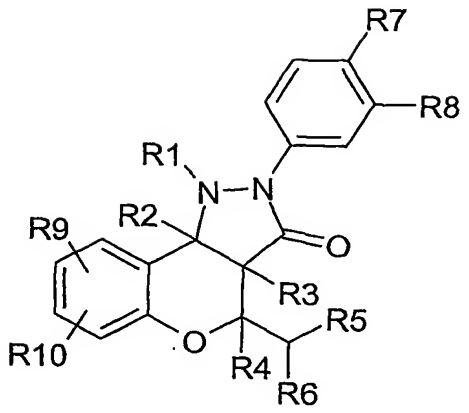
B

Compound C_is disclosed in US 4,312,870 as one of several psychoactive compounds but without biological data. Some related compounds are described by A. Carotti in Bioorganic & Medicinal Chemistry 6 (1998) 389 - 399, and from their data it is obvious that the carboxylic acid substituent greatly diminishes biologic activity measured as affinity for the CNS benzodiazepine receptor.



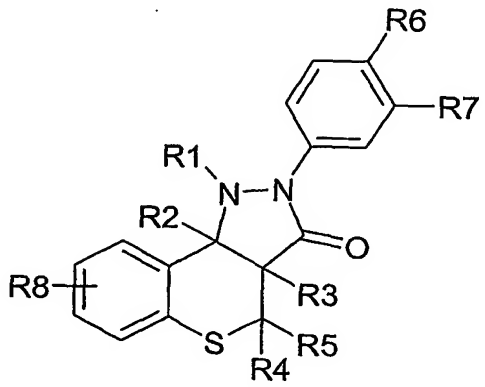
C

EP 0354693A1 (Boots) discloses immunomodulatory compounds of general structure D but does not include structures wherein R7 and/or R8 are COOH or contain a COOH group.



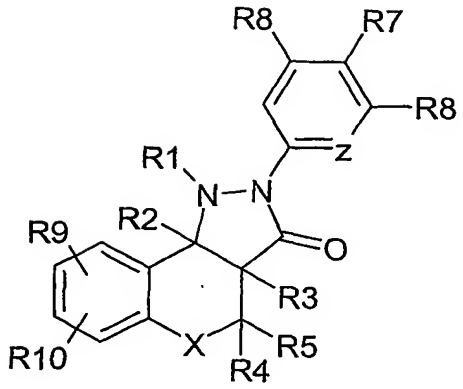
D

Similarly EP 0354694A1 (Boots) discloses immunomodulatory compounds of general structure E but here are not included structures wherein R6 and/or R7 are COOH or contain a COOH group.



E

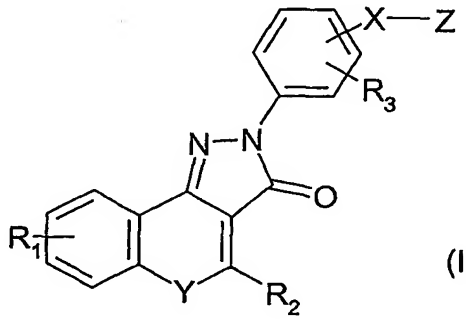
Also, WO9111448 (Boots) discloses immunomodulatory compounds of general structure F but here are not included structures wherein R7 and/or R8 and R8´ are COOH or contain a COOH group.



F

Description of the invention

According to the present invention there is provided a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof:



(I)

wherein

Z represents a carboxylic acid group (-COOH) or an ester thereof;

R_1 and R_3 independently represent H; F; Cl; Br; $-NO_2$; -CN; C_1-C_6 alkyl optionally substituted by F or Cl; or C_1-C_6 alkoxy optionally substituted by F;

R_2 represents optionally substituted C_3-C_7 cycloalkyl or optionally substituted phenyl;

Y represents -O-, -S-, N-oxide, or $-N(R_5)-$ wherein R_5 represents H or C_1-C_6 alkyl;

X represents a bond or a group selected from; a divalent C_1-C_6 alkylene radical, NHC(O) C_{1-5} alkyl, NHC(O) CH_2-O-CH_2 or C(O) -NH- (amino acid residue);

Compounds of general formula (I) are CD80 antagonists. They inhibit the interaction between CD80 and CD28 and thus the activation of T cells, thereby modulating the immune response.

Accordingly the invention also includes:

(i) a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof for use in the treatment of conditions which benefit from immunomodulation.

(ii) the use of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof in the manufacture of a medicament for the treatment of conditions which benefit from immunomodulation,.

(iii) a method of immunomodulation in mammals, including humans, comprising administration to a mammal in need of such treatment an immunomodulatory effective dose of a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof.

(iv) a pharmaceutical or veterinary composition comprising a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof together with a pharmaceutically or veterinarily acceptable excipient or carrier.

Conditions which benefit from immunomodulation include:

Acute disseminated encephalomyelitis
Adrenal insufficiency
Allergic angiitis and granulomatosis
Amylodosis
Ankylosing spondylitis
Asthma
Autoimmune Addison's disease
Autoimmune alopecia
Autoimmune chronic active hepatitis
Autoimmune hemolytic anemia
Autoimmune neutropenia
Autoimmune thrombocytopenic purpura

Behçet's disease
Cerebellar degeneration
Chronic active hepatitis
Chronic inflammatory demyelinating polyradiculoneuropathy
Chronic neuropathy with monoclonal gammopathy
Classic polyarteritis nodosa
Congenital adrenal hyperplasia
Cryopathies
Dermatitis herpetiformis
Diabetes
Eaton-Lambert myasthenic syndrome
Encephalomyelitis
Epidermolysis bullosa acquisita
Erythema nodosa
Gluten-sensitive enteropathy
Goodpasture's syndrome
Guillain-Barre syndrome
Hashimoto's thyroiditis
Hyperthyrodism
Idiopathic hemachromatosis
Idiopathic membranous glomerulonephritis
Isolated vasculitis of the central nervous system
Kawasaki's disease
Minimal change renal disease
Miscellaneous vasculitides
Mixed connective tissue disease
Multifocal motor neuropathy with conduction block
Multiple sclerosis
Myasthenia gravis
Opsoclonus-myoclonus syndrome
Pemphigoid
Pemphigus
pernicious anemia
Polymyositis/dermatomyositis
Post-infective arthritides
Primary biliary sclerosis
Psoriasis

Reactive arthritides
Reiter's disease
Retinopathy
Rheumatoid arthritis
Sclerosing cholangitis
Sjögren's syndrome
Stiff-man syndrome
Subacute thyroiditis
Systemic lupus erythematosis
Systemic necrotizing vasculitides
Systemic sclerosis (scleroderma)
Takayasu's arteritis
Temporal arteritis
Thromboangiitis obliterans
Type I and type II autoimmune polyglandular syndrome
Ulcerative colitis
Uveitis
Wegener's granulomatosis

As used herein, the term "ester" refers to a group of the form -COOR, wherein R is a radical notionally derived from the alcohol ROH. Examples of ester groups include the physiologically hydrolysable esters such as the methyl, ethyl, n- and iso-propyl, n-, sec- and tert-butyl, and benzyl esters.

As used herein the term "alkylene" refers to a straight or branched alkyl chain having two unsatisfied valencies, for example $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2CH_3)CH_2CH_2CH_3$, and $-C(CH_3)_3$.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be (C_1-C_6)alkyl, trifluoromethyl, (C_1-C_6)alkoxy (including the special case where a ring is substituted on adjacent ring C atoms by methylenedioxy or ethylenedioxy), trifluoromethoxy, (C_1-C_6)alkylthio, phenyl, benzyl, phenoxy, hydroxy, mercapto, amino, fluoro, chloro, bromo, cyano, nitro, oxo, -COOH,

$-SO_2OH$, $-CONH_2$, $-SO_2NH_2$, $-COR^A$, $-COOR^A$, $-SO_2OR^A$, $-NHCOR^A$, $-NHSO_2R^A$, $-CONHR^A$, $-SO_2NHR^A$, $-NHR^A$, $-NR^AR^B$, $-CONR^AR^B$ or $-SO_2NR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)-alkyl group, a $(C_3 - C_7)$ cycloalkyl group or $C_2 - C_6$ alkoxy group. In the case where "substituted" means substituted by benzyl or phenoxy, the phenyl ring thereof may itself be substituted with any of the foregoing, except phenyl or benzyl.

As used herein the unqualified term "carbocyclyl" or "carbocyclic" refers to a 5-8 membered ring whose ring atoms are all carbon.

Some compounds of the invention contain one or more chiral centres because of the presence of asymmetric carbon atoms. The presence of asymmetric carbon atoms gives rise to stereoisomers or diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such stereoisomers and diastereoisomers and mixtures thereof.

Salts of salt forming compounds of the invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluenesulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates; and base addition salts, for example sodium, potassium, magnesium, and calcium salts.

In the compounds of the invention the following are examples of the several structural variables:

Z may be, for example a carboxylic acid group (-COOH) or a methyl or benzyl ester thereof. Presently -COOH is preferred.

R_1 may be, for example, H, F, Cl, methyl, methoxy, or methylenedioxy. Currently it is preferred that R_1 is H, F, or Cl;

R_2 may be, for example cyclopropyl, phenyl, or fluoro-, chloro-, methyl, methoxy-, nitro-, or amino-substituted phenyl;

R_3 may be, for example, H, F, Cl, methyl, methoxy, or methylenedioxy. Currently it is preferred that R_3 is H, F, or Cl;

Y may be, for example, -O-, -S-, or -N(R_5)- wherein R_5 represents H or methyl. -NH- is presently preferred.

X may be, for example a bond, or a $-CH_2-$ or $-CH_2CH_2-$ radical. A bond is presently preferred.

As mentioned above, the invention includes pharmaceutical or veterinary composition comprising a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof together with a pharmaceutically or veterinarily acceptable excipient or carrier. In such compositions, it will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the causative organism and severity of the particular disease undergoing therapy. Optimum dose levels and frequency of dosing will be determined by clinical trial.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be

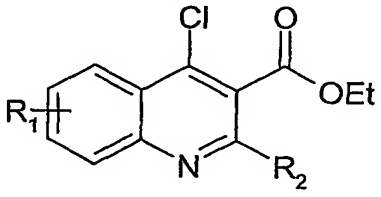
coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

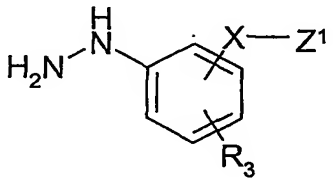
For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of the invention may be prepared by synthetic methods known in the literature, from compounds which are commercially available or are accessible from commercially available compounds. For example, compounds of formula (I) wherein Y is N may be prepared by reaction of a compound of formula (II) with an hydrazide of formula (III):



(II)

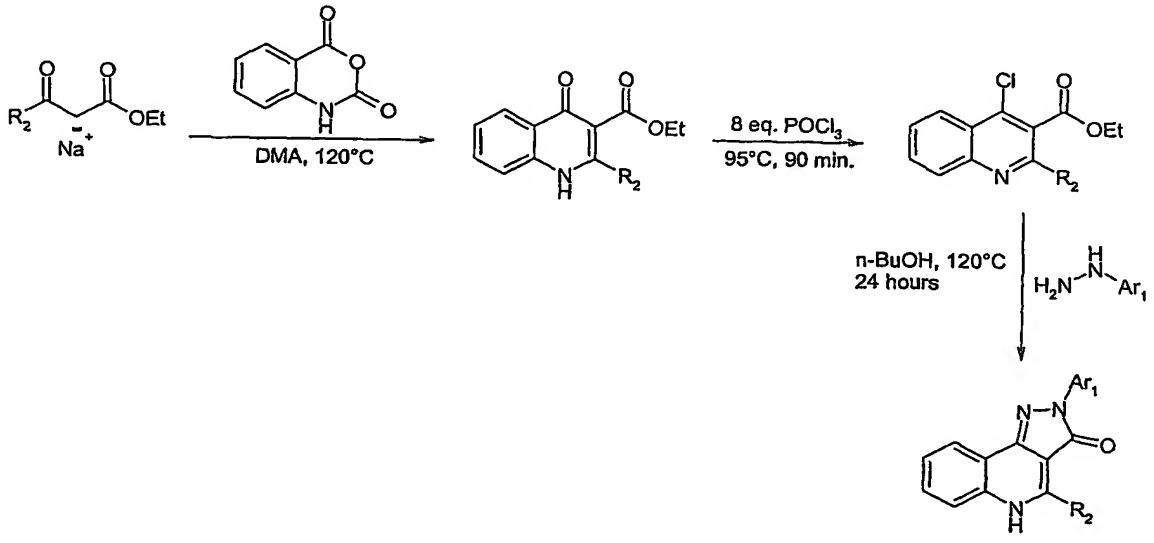


(III)

wherein Z1 is a carboxylic acid or an esterified carboxylic acid. Ester compounds (I) may of course be hydrolysed to the free acid.

The following Examples illustrate the preparation of compounds of the invention:

Synthetic route followed:

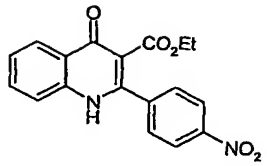


Typical experimental R_2 = 4-nitro phenyl, Ar_1 = 4-benzoic acid methyl ester

Example 1

Step 1

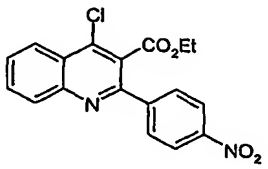
2-(4-Nitro-phenyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester



Sodium hydride (0.92 g, 0.023 mol; 60% suspension in mineral oil) was added portionwise to a stirred solution of 3-(4-nitrophenyl)-3-oxopropionic acid ethyl ester (5.46 g, 0.023 mol) in dimethylacetamide (20 mL) at room temperature. A solution of isatoic anhydride (3.4 g, 0.02 mol) in dimethylacetamide (20 mL) was added to this solution. The reddish mixture was stirred at 120 °C for 30 min and then the solvent was concentrated *in vacuo*. The crude solid was partitioned between water and ethyl acetate and the organic phase then separated. The combined organic extracts were dried over sodium sulfate and concentrated in vacuo to leave a residue which was washed once with cold tert-butylmethyl ether to yield 2-(4-nitrophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester (1.61 g, 28%) as a white solid, LCMS m/z 339.33 $[M+H]^+$ @ R_T 1.16 min, 100% purity.

Step 2

4-Chloro-2-(4-nitro-phenyl)-quinoline-3-carboxylic acid ethyl ester

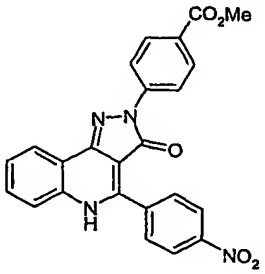


Phosphorus oxychloride (8 mL, 0.087 mol) was added in one portion to 2-(4-nitrophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid ethyl ester (3.7 g, 0.0109 mol) and the mixture was heated at 95°C for 90 min. The

resulting light brown solution was added dropwise to a vigorously stirred ice-cold solution of sodium hydroxide (500 mL; 0.7 M). The aqueous suspension was extracted with ethyl acetate and the combined organic extracts were dried and concentrated in vacuo to leave 4-chloro-2-(4-nitophenyl)-quinoline-3-carboxylic acid ethyl ester (3.8 g, 98 %) as a white solid, LCMS m/z 357.21 $[M+H]^+$ @ R_T 1.94 min, 98% purity.

Step 3

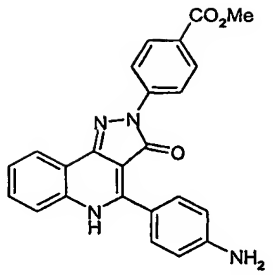
4-[4-(4-Nitro-phenyl)-3-oxo-3,5-dihydro-pyrazolo[4,3-c]quinolin-2-yl]-benzoic acid methyl ester



4-Chloro-2-(4-nitrophenyl)-quinoline-3-carboxylic acid ethyl ester (2.86 g, 0.008 mol) and 4-hydrazino-benzoic acid methyl ester hydrochloride (1.7 g, 0.008 mol) were stirred in *n*-butanol (70 mL) at 120 °C for 24 h. The bright orange suspension was diluted with tert-butylmethyl ether, filtered, washed with cold heptane and left to dry under suction to yield 4-[4-(4-nitrophenyl)-3-oxo-3,5-dihydropyrazolo[4,3-c]quinolin-2-yl]-benzoic acid methyl ester (2.7 g, 76 %) as an orange solid, LCMS m/z 441.35 $[M+H]^+$ @ R_T 1.66 min: 84% purity.

Example 2

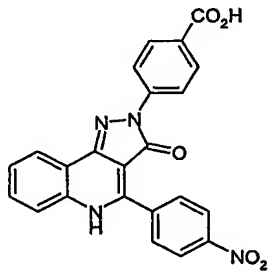
4-[4-(4-Amino-phenyl)-3-oxo-3,5-dihydro-pyrazolo[4,3-c]quinolin-2-yl]-benzoic acid methyl ester



4-[4-(4-Nitro-phenyl)-3-oxo-3,5-dihydro-pyrazolo[4,3-c]quinolin-2-yl]-benzoic acid methyl ester (2.6 g, 5.9 mmol) and Pd/C (100 mg, 10%) were suspended in ethanol (150 mL) and acetic acid (6 mL) and stirred under hydrogen for 24 h. The resulting yellow-orange suspension was diluted with DMF (50 mL) and filtered. The solvent was removed in vacuo to leave a residue which was washed with methanol to give 4-[4-(4-amino-phenyl)-3-oxo-3,5-dihydro-pyrazolo[4,3-c]quinolin-2-yl]-benzoic acid *methyl ester* (2.0 g, 82 %) as a pale orange solid, LCMS m/z 411.39 $[M+H]^+$ @ R_T 1.27 min, 79% purity.

Example 3

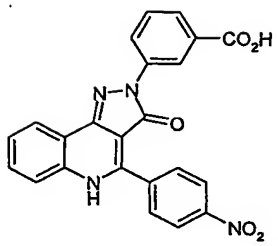
4-[4-(4-Nitro-phenyl)-3-oxo-3,5-dihydro-pyrazolo[4,3-c]quinolin-2-yl]-benzoic acid



Prepared using the procedure described above, using 4-hydrazinobenzoic acid. LCMS m/z 427.34 $[M+H]^+$ @ R_T 1.38 min, 74% purity

Example 4

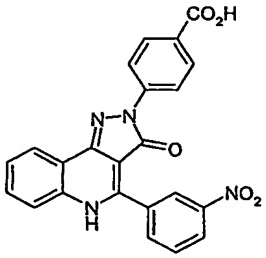
3-[4-(4-Nitro-phenyl)-3-oxo-3,5-dihydro-pyrazolo[4,3-c]quinolin-2-yl]-benzoic acid



Prepared by methods analogous to Example 3. LCMS m/z 427.37 $[M+H]^+$ @ R_T 1.28 min, 96% purity.

Example 5

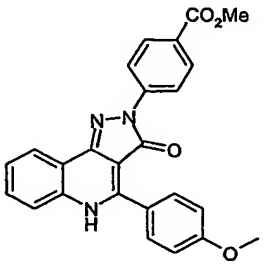
4-[4-(3-Nitro-phenyl)-3-oxo-3,5-dihydro-pyrazolo[4,3-c]-quinolin-2-yl]-benzoic acid



Prepared by methods analogous to Example 3. LCMS m/z 427.38 $[M+H]^+$ @ R_T 1.33 min, 88% purity. δ_H(400 MHz, $(CD_3)_2SO$) 12.8 (1 H, s), 8.85 (1 H, t J 2.0), 8.54 (1 H, dd J_1 7.1 J_2 2.0), 8.35 (4 H, m), 8.02 (1 H, s), 8.0 (1 H, s), 7.94 (1 H, t J 8.0), 7.84 (1 H, d J 7.9), 7.74 (1 H, t, J 7.1), 7.6 (1 H, t J 7.1).

Example 6

4-[4-(4-Methoxyphenyl)-3-oxo-3,5-dihydropyrazolo[4,3-c]quinolin-2-yl]benzoic acid methyl ester

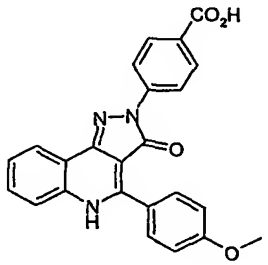


Prepared by methods analogous to Example 1. LCMS m/z 426.34 $[M+H]^+$ @ R_T 1.71 min, 82% purity. δ_H(400 MHz, $(CD_3)_2SO$) 8.2 (2 H, d J 9.0), 8.05 (1 H, dd J_1 8.0 J_2

1.1), 7.82 (2 H, d J 9.0), 7.77 (2 H, d J 9.0), 7.65 (1 H, d J 9.0), 7.48 (1 H, td J_1 8.2 J_2 1.3), 7.34 (1 H, td J_1 7.0 J_2 1.1), 6.98 (2 H, d J 9.0).

Example 7

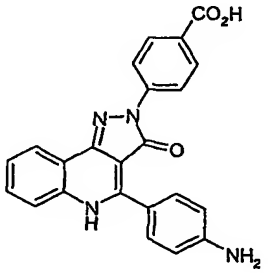
4-[4-(4-Methoxyphenyl)-3-oxo-3,5-dihydropyrazolo[4,3-c]-quinolin-2-yl]benzoic acid



Prepared using the procedure analogous to Example 1. LCMS m/z 412.28 $[M+H]^+$ @ R_T 1.28 min, 88% purity.

Example 8

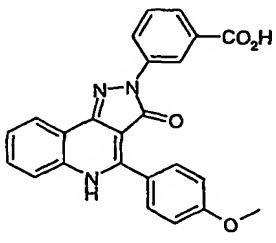
4-[4-(4-Aminophenyl)-3-oxo-3,5-dihydropyrazolo[4,3-c]-quinolin-2-yl]benzoic acid methyl ester



Prepared using the procedure analogous to Example 1. LCMS m/z 397.36 $[M+H]^+$ @ R_T 1.11 min, 63% purity.

Example 9

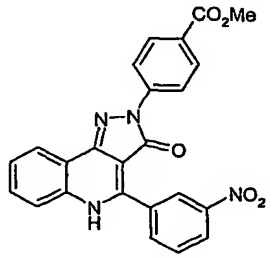
3-[4-(4-Methoxyphenyl)-3-oxo-3,5-dihydropyrazolo[4,3-c]-quinolin-2-yl]benzoic acid methyl ester



Prepared using the procedure analogous to Example 1, using 3-hydrazinobenzoic acid. LCMS m/z 412.3 $[M+H]^+$ @ R_T 1.29 min, 86% purity.

Example 10

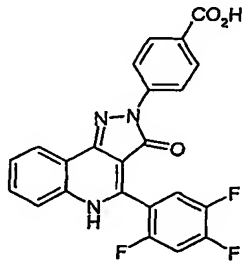
4-[4-(3-Nitrophenyl)-3-oxo-3,5-dihydropyrazolo[4,3-c]-quinolin-2-yl]benzoic acid methyl ester



Prepared by methods analogous to Example 1. LCMS m/z 441.37 $[M+H]^+$ @ R_T 1.80 min, 82% purity.

Example 11

4-[3-Oxo-4-(2,4,5-trifluorophenyl)-3,5-dihydropyrazolo-[4,3-c]quinolin-2-yl]benzoic acid



Prepared by methods analogous to Example 3. LCMS m/z 436.36 $[M+H]^+$ @ R_T 1.30 min, 83% purity.

Biological example

The examples described above were tested in a cell free Homogenous Time Resolved Fluorescence (HTRF) assay to determine their activity as inhibitors of the CD80-CD28 interaction.

In the assay, europium and allophycocyanin (APC) are associated with CD28 and CD80 indirectly (through antibody linkers) to form a complex, which brings the europium and APC into close proximity to generate a signal. The complex comprises the following six proteins:

fluorescent label 1, linker antibody 1, CD28 fusion protein, CD80 fusion protein, linker antibody 2, and fluorescent label 2. The table below describes these reagents in greater detail.

Fluorescent label 1	Anti-Rabbit IgG labelled with Europium (1μg/ml)
Linker antibody 1	Rabbit IgG specific for mouse Fc fragment (3μg/ml)
CD28 fusion protein	CD28 - mouse Fc fragment fusion protein (0.48μg/ml)
CD80 fusion protein	CD80 mouse Fab fragment (C215) fusion protein (1.9μg/ml)
Linker antibody 2	GαMκ-biotin: biotinylated goat IgG specific for mouse kappa chain (2μg/ml)
Fluorescent label 2	SA-APC: streptavidin labelled allophycocyanin (8μg/ml)

On formation of the complex, europium and APC are brought into proximity and a signal is generated.

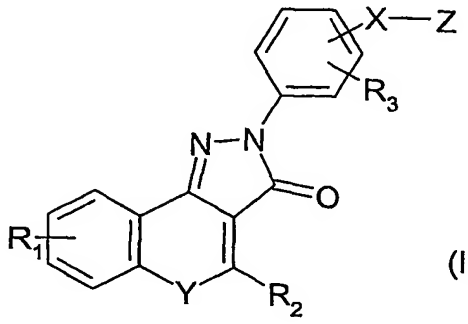
Non-specific interaction was measured by substituting a mouse Fab fragment (C215) for the CD80 mouse Fab fragment fusion protein (1.9μg/ml). The assay was carried out in black 384 well plates in a final volume of 30μl. Assay buffer: 50mM Tris-HCl, 150mM NaCl pH7.8, containing 0.1% BSA (w/v) added just prior to use.

Compounds were added to the above reagents in a concentration series ranging between 100μM - 1.7nM. The reaction was incubated for 4 hours at room temperature. Dual measurements were made using a Wallac Victor 1420 Multilabel Counter. First measurement: excitation 340nm, emission 665nm, delay 50μs, window time 200μs. second measurement: excitation 340nm, emission 615nm, delay 50μs, window time 200μs. Counts were automatically corrected for fluorescence crossover, quenching and background.

By way of illustration, the IC_{50} results for the compounds of Examples 5, 7 and 9 were 8.6 μM, 3.4 μM and 4.6 μM respectively.

CLAIMS

1. A compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof:



(I)

wherein

Z represents a carboxylic acid group (-COOH) or an ester thereof;

R_1 and R_3 independently represent H; F; Cl; Br; $-NO_2$; -CN; C_1-C_6 alkyl optionally substituted by F or Cl; or C_1-C_6 alkoxy optionally substituted by F;

R_2 represents optionally substituted C_3-C_7 cycloalkyl or optionally substituted phenyl;

Y represents -O-, -S-, N-oxide, or $-N(R_5)-$ wherein R_5 represents H or C_1-C_6 alkyl;

X represents a bond or a group selected from; a divalent C_1-C_6 alkylene radical, NHC(O) C_{1-5} alkyl or NHC(O) CH_2-O-CH_2

2. A compound as claimed in claim 1 wherein X is a bond or a $-CH_2-$ or $-CH_2CH_2-$ radical.

3. A compound as claimed in claim 1 or claim 2 wherein Z is -COOH.

4. A compound as claimed in any of the preceding claims wherein R_1 is H, F, Cl, methyl, methoxy, or methylenedioxy.

5. A compound as claimed in any of the preceding claims wherein R_2 is cyclopropyl, phenyl, or fluoro-, chloro-, methyl, methoxy-, nitro-, or amino- substituted phenyl

6. A compound as claimed in any of the preceding claims wherein R_3 is H, F, Cl, methyl, methoxy, or methylenedioxy.

7. A compound as claimed in any of the preceding claims wherein Y is $-N(R_5)-$ wherein R_5 represents H or methyl.

8. A compound as claimed in any of claims 1 to 7 for use in the treatment of conditions which benefit from immunomodulation.

9. The use of a compound as claimed in any of claims 1 to 7 in the manufacture of a medicament for the treatment of conditions which benefit from immunomodulation.

10. A method of immunomodulation in mammals, including humans, comprising administration to a mammal in need of such treatment an immunomodulatory effective dose of a compound as claimed in any of claims 1 to 9.

11. A pharmaceutical or veterinary composition comprising a compound as claimed in any of claims 1 to 9 together with a pharmaceutically or veterinarily acceptable excipient or carrier.

INTERNATIONAL SEARCH REPORT

Intern... application No.
PCT/SE 2003/001941

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 471/04, A61K 31/437, A61P 37/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03004495 A1 (ACTIVE BIOTECH AB), 16 January 2003 (16.01.2003), see the whole document	1-11
X	WO 9111448 A1 (THE BOOTS COMPANY PLC), 8 August 1991 (08.08.1991), see page 29, lines 10-24 and the claims	1-11
X	WO 9734893 A1 (ASTRA PHARMACEUTICALS LTD.), 25 August 1997 (25.08.1997), see page 15, lines 12-35 and the claims	1-11

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2004	22 -03- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer NEBIL GECER/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/01941

Box No. II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/01941

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Claim 10 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic methods practised on the human or animal body/Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001941

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0354693 A1 (THE BOOTS COMPANY PLC.), 14 February 1990 (14.02.1990), see page 7, lines 10-17 and the claims	1-11

INTERNATIONAL SEARCH REPORT
Information on patent family members

27/02/2004

Internauonal application No.
PCT/SE 2003/001941

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				ZA	9100764 A	30/10/1991
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INTERNATIONAL SEARCH REPORT

Information on patent family members

27/02/2004

International application No.
PCT/SE 2003/001941

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				IL	126271	D	00/00/0000
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				NO	984290	A	27/10/1998
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				GB	9610894	D	00/00/0000
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				BR	9708478	A	13/04/1999
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				DK	88790	A	09/04/1990
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				NZ	230231	A	26/03/1992
				PH	26314	A	29/04/1994
				PT	91408	A	08/03/1990
				WO	9001481	A	22/02/1990
				YU	155189	A	28/02/1991
				ZA	8905646	A	25/04/1990
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